AMENDMENTS TO THE CLAIMS

1. (Original) An immunogen, characterized in that said immunogen comprises a polypeptide sequence comprising amino acid sequence 1, amino acid sequence 2 and amino acid sequence 3, and these amino acid sequences 1, 2 and 3 are covalently linked together by linking peptides consisting of several amino acid residues; said amino acid sequence 1 is the sequence of Th cell epitope; said amino acid sequence 2 is the sequence of a CTL epitope from hepatitis B virus; and said amino acid sequence 3 is the sequence of B cell epitope from hepatitis B virus.

2. (Previously presented) An immunogen according to Claim 1, characterized in that said amino acid sequence 1 is the amino acid sequence at position 830-843 of the Th cell epitope derived from tetanus toxoid or variant sequences thereof, or the universal Th cell epitope of PADRE; said amino acid sequence 2 is the amino acid sequence of position 18-27 of the HBV core antigen or variant sequences thereof, the amino acid sequence of position 141-151 of the HBV core antigen or variant sequences thereof, the amino acid sequence of position 117-125 of the HBV core antigen or variant sequences thereof, the amino acid sequence of position 88-94 of the HBV core antigen or variant sequences thereof, the amino acid sequence of position 88-96 of the HBV core antigen or variant sequences thereof, the amino acid sequence of position 183-191 of the HBV surface antigen or variant sequences thereof, the amino acid sequence of position 201-210 of the HBV surface antigen or variant sequences thereof, the amino acid sequence of position 204-212 of the HBV surface antigen or variant sequences thereof, the amino acid sequence of position 370-379 of the HBV surface antigen or variant sequences thereof, the amino acid sequence of position 251-259 of the HBV surface antigen or variant sequences thereof, the amino acid sequence of position 260-269 of the HBV surface antigen or variant sequences thereof, the amino acid sequence of position 335-343 of the HBV surface

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antigen or variant sequences thereof, the amino acid sequence of position 338-347 of the HBV surface antigen or variant sequences thereof, the amino acid sequence of position 348-357 of the HBV surface antigen or variant sequences thereof, the amino acid sequence of position 378-387 of the HBV surface antigen or variant sequences thereof; the amino acid sequence at position 10-17 of the Pre S1 antigen or variant sequences thereof, the amino acid sequence at position 109-123 of the Pre S2 antigen or variant sequences thereof, the amino acid sequence at position 152-161 or variant sequences thereof; the amino acid sequence at position 92-100 of the HBx antigen or variant sequences thereof, the amino acid sequence at position 99-108 of the HBx antigen or variant sequences thereof, the amino acid sequence at position 115-123 of the HBx antigen or variant sequences thereof, the amino acid sequence at position 133-141 of the HBx antigen or variant sequences thereof; the amino acid sequence at position 61-69 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 455-463 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 575-583 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 773-782 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 803-811 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 756-764 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 816-824 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 655-663 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 551-559 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 772-780 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 502-510 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 538-546 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 642-650 of the Pol antigen or variant sequences thereof, the amino acid sequence at position 646-654 of the Pol

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antigen or variant sequences thereof, and said amino acid sequence 3 is the amino acid sequence at position 14-24 of the B cell epitope derived from HBV Pre-S2 or variant sequences thereof, or the determinant a of HBS antigen.

3. (Previously presented) An immunogen according to Claim 1, characterized in that said amino acid sequence 1 is QYIKANSKFIGITE (SEQ ID NO:6) or variant sequences thereof, PADRE (SEQ ID NO:7) or variant sequences thereof; said amino acid sequence 2 is PLGFFPDH (SEQ ID NO:8) or variant sequences thereof, MQWNSTALHQALQDP (SEQ ID NO:9) or variant sequences thereof, SILSKTGDPV (SEQ ID NO:10) or variant sequences thereof, VLQAGFFLL (SEQ ID NO:11) or variant sequences thereof, FLLTRILTI (SEQ ID NO:12) or variant sequences thereof, FLGGTPVCL (SEQ ID NO:13) or variant sequences thereof, LLCLIFLLV (SEQ ID NO:14) or variant sequences thereof, LLDYQGMLPV (SEQ ID NO:15) or variant sequences thereof, WLSLLVPFV (SEQ ID NO:16) or variant sequences thereof, GLSPTVWLSV (SEQ ID NO:17) or variant sequences thereof, KVLHKRTLGL (SEQ ID NO:18) or variant sequences thereof, VLHKRTLGL (SEQ ID NO:19) or variant sequences thereof, GLSAMSTTDL (SEQ ID NO:20) or variant sequences thereof, CLFKDWEEL (SEQ ID NO:21) or variant sequences thereof, VLGGCRHKLV (SEQ ID NO:22) or variant sequences thereof, FLPSDFFPSV (SEQ ID NO:23) or variant sequences thereof, STLPETTVVRR (SEQ ID NO:24) or variant sequences thereof, EYLVSFGVW (SEQ ID NO:25) or variant sequences thereof, GLYSSTVPV (SEQ ID NO:26) or variant sequences thereof, GLSRYVARL (SEQ ID NO:27) or variant sequences thereof, FLLSLGIHL (SEQ ID NO:28) or variant sequences thereof, ILRGTSFVYV (SEQ ID NO:29) or variant sequences thereof, SLYADSPSV (SEQ ID NO:30) or variant sequences thereof, KYTSFPWLL (SEQ ID NO:31) or variant sequences thereof, SLYADSPSV (SEQ ID NO:32) or variant sequences thereof, ALMPLYACI (SEQ ID NO:33) or variant sequences thereof,

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YMDDVVLGA (SEQ ID NO:34) or variant sequences thereof, WILRGTSFV (SEQ ID NO:35) or variant sequences thereof, KLHLYSHPI (SEQ ID NO:36) or variant sequences thereof, FTQAGYPAL (SEQ ID NO:37) or variant sequences thereof, SLNFLGGTTV (SEQ ID NO:38) or variant sequences thereof, LLDYQGMLPV (SEQ ID NO:39) or variant sequences thereof, LLVPFVQWFV (SEQ ID NO:40) or variant sequences thereof, GLSPTVWLSV (SEQ ID NO:41) or variant sequences thereof, LLPIFFCLWV (SEQ ID NO:42) or variant sequences thereof, YVNTNMG (SEQ ID NO:43) or variant sequences thereof, YVNTNMGLK (SEQ ID NO:44) or variant sequences thereof, SILSKTGDPV (SEQ ID NO:45) or variant sequences thereof, GLSPTVWLSV (SEQ ID NO:46) or variant sequences thereof, SIVSPFIPLL (SEQ ID NO:47) or variant sequences thereof; and said amino acid sequence 3 is DPRVRGLYFPA (SEQ ID NO:48) or variant sequences thereof, or CTKPTDGNCT (SEQ ID NO:49) or variant sequences thereof.

4. (Previously presented) An immunogen according to Claim 1, characterized in that said linking peptide consists of 3-7 amino acid residues.

5. (Previously presented) An immunogen according to Claim 1, characterized in that the linking peptide is AAA, SSS or GGG.

6. (Previously presented) An immunogen according to Claim 1, characterized in that the order for linking the amino acid sequence 1, the amino acid sequence 2 and the amino acid sequence 3 is amino acid sequence 1-amino acid sequence 2-amino acid sequence 3, amino acid sequence 1-amino acid sequence 3-amino acid sequence 2, amino acid sequence 2-amino acid sequence 1-amino acid sequence 3, amino acid sequence 2-amino acid sequence 3-amino acid sequence 1, amino acid sequence 3-amino acid sequence 1-amino acid sequence 2, or amino acid sequence 3-amino acid sequence 2-amino acid sequence 1.

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7. (Previously presented) An immunogen according to Claim 1, characterized in that said immunogen further comprises several modifying groups which can be alkylcarbonyl groups, or alkenylcarbonyl groups.

8. (Previously presented) An immunogen according to Claim 1, characterized in that said immunogen further comprises two modifying groups.

9. (Previously presented) An immunogen according to Claim 1, characterized in that said immunogen further comprises one modifying group.

10. (Previously presented) An immunogen according to Claim 7, characterized in that said alkylcarbonyl is one to five alkylcarbonyl groups selected from a group consisting of $CH_3(CH_2)_{10}CO$—, $CH_3(CH_2)_{12}CO$—, $CH_3(CH_2)_{14}CO$— and $CH_3(CH_2)_{16}CO$—; and the said alkenylcarbonyl is one or five alkenylcarbonyl groups selected from a group consisting of $CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$—, $CH_3CH_2CH{=}CHCH_2CH{=}CH$—$(CH_2)_7CO$— and $CH_3CH_2CH{=}CHCH_2CH{=}CH(CH_2)CH{=}CH(CH_2)_7CO$—.

11. (Previously presented) An immunogen according to Claim 9, characterized in that said modifying group is covalently linked to any amino acid residue of said polypeptide sequence.

12. (Previously presented) An immunogen according to Claim 9, characterized in that said modifying group is covalently linked to an N-terminal α-amino group, a C-terminal α-carboxyl group or any side chain group of an amino acid residue of said polypeptide sequence.

13. (Currently amended) An immunogen according to Claim 12, characterized in that said modifying group is linked to an N-terminal α-amino group of said polypeptide sequence via

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a linking peptide KSS, wherein the N-terminal α-amino group is linked to the C-terminus of the linking peptide KSS via a peptide bond, and said modifying group is covalently linked to the ~~epsilon-amino~~ ε-amino group on the linking peptide KSS.

14. (Previously presented) An immunogen according to Claim 12, characterized in that said modifying group is covalently linked to an amino group, carboxyl group or hydroxyl group on said side chain group.

15. (Previously presented) An immunogen according to Claim 12, characterized in that said modifying group is covalently linked to the ε-amino group on the N-terminal lysine.

16. (Currently amended) An immunogen according to Claim 13, characterized in that the ~~a-amino~~ α-amino group of said linking peptide KSS is further covalently linked to one of said modifying groups.

17. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{10}$COKSSPADREGGGSLNFLGGTTVSSSDPRVRGLYFPA (SEQ ID NO:50).

18. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{14}$COKSSQYIKANSKFIGITEAAALLCLIFLLVGGGDPRVRGLYFPA (SEQ ID NO:51).

19. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{16}$COKSSPADREAAALLDYQGMLPVGGGDPRVRGLYFPA (SEQ ID NO:52).

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20. (Currently amended) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_7CH=CH(CH_2)$—CO[[,]] $CH_3CH_2CH=CHCH_2CH=CH(CH_2)_7CO_7$KSSQYIKANSKFIGITEGGG (SEQ ID NO:53).

21. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3CH_2CH=CHCH_2CH=CH(CH_2)CH=CH(CH_2)_7$COFLPSDFFPSVAAADPRVRGLYFPA (SEQ ID NO:54).

22. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3CH_2CH=CHCH_2CH=CH(CH_2)CH=CH(CH_2)_7$COKSSPADREGGGWLSLLVPFVSSSDPRV RGLYFPA (SEQ ID NO:55).

23. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{14}$COKSSQYIKANSKFIGITEAAAFLPSDFFPSVGGGDPRVRGLYFPA (SEQ ID NO:1).

24. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{14}$COKSSPADREAAAFLPSD FFPSVGGGDPRVRGLYFPA (SEQ ID NO:56).

25. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{14}$COKSSPADREGGGLLVPFVQWFVSSSDPRVRGLYFPA (SEQ ID NO:57).

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26. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{14}$COKSSPADREAAAGLSPTVWLSVGGGDPRVRGLYFPA (SEQ ID NO:58).

27. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{16}$COKSSPADREAAALLPIFF CLWVGGGDPRVRGLYFPA (SEQ ID NO:59).

28. (Currently amended) An immunogen according to Claim 1, characterized in that the primary structure thereof is ~~thereof~~ $CH_3(CH_2)_{16}$COKSSQYIKANSKFI GITEAAAYVNTNMGGGGDPRVRGLYFPA (SEQ ID NO:60).

29. (Currently amended) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{16}$COKSSQYIKANSKFIGITEAAAFLPSDFFPSVGGGDPRVRGLYFPA (SEQ ID NO:[[1]] 74).

30. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{14}$COKSSQYIKANSKFIGITEGGGFLPSDFFPSVSSSDPRVRGLYFPA (SEQ ID NO:61).

31. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{14}$COKSSQYIKANSKFIGITEAAAYVNTNMGLKGGGDPRVRGLYFPA (SEQ ID NO:62).

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32. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{14}$COKSSQYIKANSKFIGITEAAAPLGFFPDHGGGDPRVRGLYFPA (SEQ ID NO:63).

33. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{14}$COKSSQYIKANSKFIGITEAAAMQWNSTALHQALQDPGGGDPRVRGLYFPA (SEQ ID NO:64).

34. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{14}$COKSSPDAREAAASILSKTGDPVGGGDPRVRGLYFPA (SEQ ID NO:65).

35. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{16}$COKSSPADREAAAVLQAGFFLLGGGDPRVRGLYFPA (SEQ ID NO:66).

36. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{16}$COKSSPADRESSSFLLTRILTIGGGDPRVRGLYFPA (SEQ ID NO:67).

37. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{16}$COKSSPADREAAAFLGGTPVCLGGGDPRVRGLYFPA (SEQ ID NO:68).

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38. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{14}$COKSSQYIKANSKFIGITEAAAGLSPTVWLSVGGGDPRVRGLYFPA (SEQ ID NO:69).

39. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{14}$COKSSQYIKANSKFIGITEAAASIVSPFIPLLGGGDPRVRGLYFPA (SEQ ID NO:5).

40. (Previously presented) An immunogen according to Claim 1, characterized in that the primary structure thereof is $CH_3(CH_2)_{16}$COKSSPADREAAASTLPETTVVRRGGGDPRVRGLYFPA (SEQ ID NO:70).

41. (Currently amended) An immunogen according to Claim 1, characterized in that the primary structure thereof is CH_3[[—]]$(CH_2)_{14}$COKSSQYIKANSKFIGITEAAAFLPSDFFPSVGGGCTKPTDGNCT (SEQ ID NO:4).

42. (Withdrawn) A method for designing, screening and synthesizing an immunogen according to Claim 1, comprising epitope-based vaccine design (EBVD), molecular simulation, molecular design, screening system and solid-phase synthesis of polypeptide, wherein in the polypeptide solid-phase synthesis, the molar ratio of resin to each amino acid or palmitic acid feed is from 1:2 to 1:8, the double coupling is used for linking arginine, asparagine and palmitic acid component, and the reaction temperature is from 20° to 40°C.

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43. (Withdrawn) The method of Claim 42, wherein the molar ratio of resin to each amino acid or palmitic acid feed is 1:4, and the reaction temperature is 30°C.

44. (Withdrawn) A method for preparing an immunogen according to Claim 1, characterized in that said method comprises the following steps: (1) synthesizing an immunogen-resin by polypeptide solid synthesis, wherein said immunogen-resin represents the immunogen bound to resin; (2) cleaving said immunogen-resin to obtain a cleavage solution; (3) preliminarily purifying the cleavage solution of the step (2) by size exclusion chromatography; and (4) purifying by reversed phase chromatography to obtain the immunogen.

45. (Withdrawn) The method of Claim 44, characterized in that TFA cleaving solution is used in the step (2), and the cleavage conditions are that the concentration of the immunogen-resin is lower than 100 mg/ml, the reaction temperature is from 15° to 50°C., and the reaction time is from 0.5 to 3 hours.

46. (Withdrawn) The method of Claim 44, characterized in that said TFA cleaving solution is composed of 0.75 g phenol, 0.25 ml dithioglycol, 0.5 ml phenyl methyl thioether, 0.5 ml deionized water, and 10.0 ml TFA; and said cleavage conditions are that the concentration of the immunogen-resin is 40 mg/ml, the reaction temperature is 25°C., and the reaction time is 1.5 hours.

47. (Withdrawn) The method of Claim 44, characterized in that in the size exclusion chromatography in the step (3), Sephadex LH20 is used as the column packing, and dimethyl sulphoxide is used as the mobile phase.

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48. (Withdrawn) The method of Claim 44, characterized in that in the reversed phase chromatography in the step (4), POROS 50 R1, POROS 50R2, SOURCE 30 RPC or Delta Pak C18 is used as column packing.

49. (Withdrawn) The method of Claim 44, characterized in that gradient eluting is employed in the reversed phase chromatography in step (4), wherein the mobile phase is an aqueous solution of acetonitrile/TFA, acetonitrile/HCl, ethanol/TFA, ethanol/HCl or ethanol/phosphoric acid.

50. (Withdrawn) The method of Claim 44, characterized in that the column temperature of said reversed phase chromatography is from 20° to 60°C.

51. (Withdrawn) The method of Claim 50, characterized in that the column temperature of said reversed phase chromatography is from 28° to 40°C.

52. (Withdrawn) The method of Claim 51, characterized in that the column temperature of said reversed phase chromatography is from 32° to 36°C.

53. (Withdrawn) The method of Claim 52, characterized in that the column temperature of said reversed phase chromatography is 34°C.

54. (Currently amended) ~~Use of~~ A vaccine comprising an immunogen according to Claim 1, wherein the vaccine is suitable ~~in the manufacture of a vaccine or a medicament~~ for treatment of [[the]] a chronic HBV persistent infection state and [[the]] relevant secondary diseases ~~such as~~ selected from the group consisting of liver cirrhosis [[or]] and liver cancer.

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55. (Currently amended) ~~Use according to~~ The vaccine of Claim 54, ~~characterized in that said~~ wherein the chronic HBV persistent infection state occurs in a patient with chronic hepatitis B or a carrier of hepatitis B virus.

56. (Previously presented) A vaccine for treatment of hepatitis B, characterized in that said vaccine comprises an immunogen according to Claim 1.

57. (Previously presented) A vaccine for treatment of hepatitis B, characterized in that said vaccine comprises an immunogen according to Claim 1 and pharmaceutically acceptable auxiliary materials, adjuvants and/or carriers.

58. (Previously presented) A vaccine for treatment of hepatitis B according to Claim 54, characterized in that said vaccine is in any pharmaceutically acceptable formulation.

59. (Previously presented) A vaccine for treatment of hepatitis B according to Claim 54, characterized in that the formulation of said vaccine is injection formulation, percutaneous formulation, oral formulation, inhalant formulation or suppository formulation.

60. (Previously presented) A vaccine for treatment of hepatitis B according to Claim 58, characterized in that said vaccine is in liquid dosage form, suspension dosage form, liquid liposome dosage form or lyophilized liposome dosage form.

61. (Previously presented) A vaccine for treatment of hepatitis B according to Claim 60, characterized in that said liquid dosage form is an ethanol solution dosage form.

62. (Previously presented) A vaccine for treatment of hepatitis B according to Claim 60, characterized in that said liquid liposome dosage form or lyophilized liposome dosage form comprises phospholipids.

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63. (Previously presented) A vaccine for treatment of hepatitis B according to Claim 62, characterized in that said liquid liposome dosage form or lyophilized liposome dosage form further comprises cholesterol.

64. (Previously presented) A vaccine for treatment of hepatitis B according to Claim 62, characterized in that said liquid liposome dosage form or lyophilized liposome dosage form further comprises vitamin E.

65. (Previously presented) A vaccine for treatment of hepatitis B according to Claim 62, characterized in that said liquid liposome dosage form or lyophilized liposome dosage form further comprises palmitic acid.

66. (Previously presented) A vaccine for treatment of hepatitis B according to Claim 60, characterized in that the molar ratio of immunogen : phospholipids : cholesterol : vitamin E : palmitic acid in the vaccine is 0.1-0.5 : 40-80 : 0-40 : 0-10 : 0-10.

67. (Previously presented) A vaccine for treatment of hepatitis B according to Claim 66, characterized in that the molar ratio of immunogen : phospholipids : cholesterol : vitamin E : palmitic acid in the vaccine is 0.2-0.4 : 60 : 20 : 6 : 6.

68. (Currently amended) A vaccine for treatment of hepatitis B according to Claim 67, characterized in that the molar ratio of immunogen : phospholipids : cholesterol : vitamin E : palmitic acid in the vaccine is 0.3-0.36 : 60 : 20 : 6 : 6.

69. (Previously presented) A vaccine for treatment of hepatitis B according to Claim 60, characterized in that said phospholipids are soybean phospholipids or lecithin.

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70. (Withdrawn) A method for preparing a vaccine for treatment of hepatitis B according to Claim 60, characterized in that said method comprises using double emulsifying method to prepare the liposome.

71. (Previously presented) A vaccine for treatment of hepatitis B according to Claim 60, characterized in that said lyophilized liposome dosage form further comprises human albumin, mannitol and phosphates.

72. (Currently amended) A vaccine for treatment of hepatitis B according to Claim 60, characterized in that said lyophilized liposome dosage form comprises an immunogen according to Claim 1, phospholipids, cholesterol, palmitic acid, vitamin E, mannitol, human albumin, KH_2PO_4 and Na_2PO_4 in a molar ratio of 0.01-0.1 : 5-15 : 1-7 : 0.5-1.5 : 0.5-1.5 : 70-150 : 0.1-0.3 : 1-10 : 1-10.

73. (New) A method for treatment of a chronic HBV persistent infection state and secondary diseases selected from the group consisting of liver cirrhosis and liver cancer, comprising administering an immunogen according to Claim 1 to a subject in need thereof.

74. (New) The method of Claim 73, wherein the chronic HBV persistent infection state occurs in a patient with chronic hepatitis B or a carrier of hepatitis B virus.

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